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Prevention of Venous Thromboembolism in Pancreatic Cancer: Breaking Down a Complex Clinical Dilemma

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Abstract

Venous thromboembolism (VTE) frequently occurs in patients with cancer, and particularly those with pancreatic ductal adenocarcinoma (PDAC). Therapeutic anticoagulation with either low-molecular-weight heparin or a direct oral anticoagulant is clearly beneficial in patients who develop a VTE. However, whether thromboprophylaxis improves patient outcomes remains unclear. Studies assessing this risk show a 10%–25% risk of VTE, with reduction to 5%–10% with thromboprophylaxis but no impact on survival. To aid in the risk stratification of patients, several tools have been developed to identify those at highest risk for a VTE event. However, the clinical application of these risk stratification models has been limited, and most patients, even those at the highest risk, will never have a VTE event. New oral anticoagulants have greatly improved the feasibility of prophylaxis but do show increased risk of bleeding in patients with the underlying gastrointestinal dysfunction frequently found in patients with pancreatic cancer. Recently, several completed clinical trials shed new light on this complicated risk versus benefit decision. Here, we present this recent evidence and discuss important considerations for the clinician in determining whether to initiate thromboprophylaxis in patients with PDAC. ***The Oncologist*** 2020;25:132–139

Implications for Practice: Given the high risk of venous thromboembolism in patients with pancreatic adenocarcinoma (PDAC), whether to initiate prophylactic anticoagulation is a complex clinical decision. This review discusses recent evidence regarding the risk stratification and treatment options for thromboprophylaxis in patients with PDAC, with the goal of providing practicing clinicians with updates on recent developments in the field. This article also highlights important considerations for individualizing the treatment approach for a given patient given the lack of general consensus of uniform recommendations for this patient population.

Introduction

Patients with pancreatic cancer are at significantly increased risk of developing a venous thromboembolism (VTE) during their disease course. However, whether primary prevention using anticoagulants can successfully decrease VTE risk and improve outcomes for patients with pancreatic cancer remains controversial. In addition, patients with pancreatic cancer often experience a complex disease and treatment course with pancreatectomy for resectable disease and intensive chemotherapy for advanced disease. Thromboembolism risk as well as bleeding risk fluctuate during a patient's disease course, making it challenging for clinicians to determine when to consider thromboprophylaxis. In this review, we discuss the prevention and management of VTE, specifically in patients with pancreatic cancer.

Pathophysiology and Epidemiology of Pancreatic Cancer and Venous Thromboembolism

Pancreatic cancer represents one of the most prothrombotic malignancies, with an incidence of VTE of approximately 20% [1]. Several studies also suggest that the development of VTE is associated with a worse prognosis, although this remains controversial [2, 3]. A number of distinct mechanisms appear to mediate this risk, and the cancer-associated hypercoagulable state involves a complex interplay between platelets, coagulation factors, and key inflammatory pathways. In pancreatic cancer, tissue factor (TF), also called CD142, in particular appears to play a central role in promoting a prothrombotic state. Both preclinical and clinical studies demonstrate that pancreatic tumors

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Table 1. Khorana, Vienna, and PROTECHT Scores for predicting VTE risk in patients with cancer

Characteristic	Khorana score	Vienna score	PROTECHT score
Cancer site			
Very high risk (stomach, pancreas)	2	2	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1	1	1
Labs			
Prechemotherapy platelet count ≥350,000/mm^3	1	1	1
Hemoglobin <10g/dL or use of erythropoiesis-stimulating agents	1	1	1
Prechemotherapy leukocyte count ≥11,000/mm^3	1	1	1
Body mass index ≥35 kg/m^2	1	1	1
Additional labs for the Vienna Score			
D-dimer >1.44 μg/mL		1	
Soluble P-selectin >53.1 mg/mL		1	
Additional characteristics for the PROTECHT score			
Platinum chemotherapy			1
Gemcitabine chemotherapy			1

The Khorana score includes cancer site, prechemotherapy platelet count, hemoglobin, prechemotherapy leukocyte count, and body mass index to divide patients into low-, intermediate-, and high-risk groups. The Vienna score adds D-Dimer and soluble P-selectin levels to variables in the Khorana score. The PROTECHT score adds use of chemotherapy agents to the Khorana score.

produce high levels of TF, encoded by the F3 gene, which are secreted into the circulation in membrane vesicles. TF promotes a prothrombotic state, binding to factor VIIa, which then mediates the conversion of factor X to Xa and of factor IX to IXa [4]. In addition, in pancreatic tumors, the activity of TF can be potentiated by increased tumor endothelial surface expression of anionic phospholipids and increased production of heparanase. Other biological mechanisms that further promote clot formation include secretion of cancer procoagulant, a protease that directly activates factor X; proinflammatory cytokines that stimulate expression of prothrombotic proteins within the vascular endothelium; mucin production; fibrin deposition; and platelet aggregation [5]. Along with promoting a hypercoagulable state, these mechanisms likely also provide a survival advantage to cancer cells by providing proliferative signals and stimulating angiogenesis within the tumor microenvironment.

Risk Stratification for VTE in Patients with Pancreatic Cancer

Given that the majority of patients with pancreatic cancer will not develop a VTE, further elucidation of patient, treatment, and tumor-specific factors that increase thrombotic risk are essential to identifying patients who could benefit from thromboprophylaxis. Several risk stratification schema have been developed to identify patients with cancer at the highest risk for VTE. The most well-established and validated model is the Khorana score, which was based on a cohort of 3,000 patients participating in the Awareness of Neutropenia in Chemotherapy (ANC) Study Group Registry [6, 7]. Key risk factors from this analysis included site of cancer (with pancreas and stomach cancer conferring the highest risk), prechemotherapy platelet count, hemoglobin, use of red blood cell growth factors, leukocyte count, and body mass index (Table 1). Although the model has been validated in multiple cohorts [8–10], its generalizability to all tumor types remains controversial. For example, when applied to a cohort of patients with lung cancer, there was no difference in VTE events between those with intermediate and high-risk Khorana scores [11], and the models do not differentiate well among patients with pancreatic cancer. Several modifications to this model have been proposed, including the addition of D-dimer by the Vienna CATS group or the inclusion of certain concurrent chemotherapy agents (platinum-based therapy and gemcitabine) in the PROTECHT score (Table 2) [12]. A significant limitation of current risk stratification models is their relatively low positive predictive value, which limits their utility in determining which patients are most likely to benefit from thromboprophylaxis, as most patients even with high-risk scores will never have a thrombosis. These risk stratification models also fail to capture additional important factors such as history of VTE or presence of another hypercoagulable state, which are important considerations when weighing risk versus benefit of anticoagulation.

Although the association of VTE risk with stage varies across cancer types, in pancreatic cancer, risk appears to correlate with the presence of metastatic disease [13]. The apparent association between disease burden and VTE risk raised the question of whether the CA19-9 tumor marker can be incorporated into risk stratification models. CA19-9, or sialyl Lewis antigen, is a carbohydrate structure modifying a number of proteins including mucins [14]. Potentially prothrombogenic itself, CA19-9 is overexpressed by pancreatic cancer cells, with the actual level controlled by several factors, including tumor burden, differentiation of the tumor, expression of the glycoproteins being modified, and genetic variation in the fucosyltransferases FUT2 and FUT3 [15–17]. In addition, 8% of patients have a homozygous nonfunctional variant of FUT3 that precludes synthesis of CA19-9 [15]. Although retrospective studies suggest

Table 2. Risk of VTE by Khorana, Vienna, or PROTECHT score

Khorana score			Vienna score		PROTECHT score	
Total score	VTE risk	Rate of symptomatic VTE	Total score	Rate of symptomatic VTE	Total score	Rate of symptomatic VTE
0	Low	0.3%–0.8%	0	1.0%	0–2	2.0%–4.7%
1–2	Intermediate	1.8%–2.0%	1	4.4%	≥3	9.6%–11.1%
≥3	High	6.7%–7.1%	2	3.5%		
			3	10.3%		
			4	20.3%		
			≥5	35%		

Abbreviation: VTE, venous thromboembolism.

a significant association between median CA19-9 level and VTE events, CA 19-9 has not been integrated or validated in predictive models of VTE risk and therefore currently is not included in the thromboprophylaxis decision [18–20].

Chemotherapy exposure is also thought to independently increase risk of thromboembolism in patients with pancreatic cancer [21, 22]. Although the mechanisms underlying this increased risk are poorly understood, cytotoxic chemotherapy can lead to damage to endothelial cells, promoting clot formation and altering expression of coagulation factors, which can further enhance the hypercoagulable state associated with malignancy [23, 24]. There are likely additional mechanisms that vary by agent used. In addition, patient factors including decreased mobility and performance status during chemotherapy may further increase thrombotic risk during chemotherapy treatment.

Given that surgery is the only curative approach, neoadjuvant chemotherapy plays an important role for patients with borderline resectable or locally advanced pancreatic cancer who could be surgical candidates if a sufficient decrease in tumor size is achieved. Although no data show that thromboprophylaxis can increase survival, data do suggest that patients who develop thromboembolism during neoadjuvant therapy are approximately 60% less likely to complete treatment, including surgical resection, than patients who do not develop a thromboembolism [25]. Thromboprophylaxis may therefore contribute to the long-term survival of this population of patients and should be carefully considered for patients undergoing neoadjuvant chemotherapy.

There is consensus regarding thromboprophylaxis in the immediate postoperative period after pancreatectomy, one of the highest risk periods for VTE for patients with pancreatic cancer [7]. Overall, the risk of thromboembolism (approaching 5%) is thought to outweigh the risk of postpancreatectomy anticoagulant-associated hemorrhage in the first 30 postoperative days for most patients. The highest risk appears to be approximately 7 days postoperatively, but up to one-third of VTE events after pancreatectomy occur after discharge from the hospital. A new model developed by Beal et al. aimed to further stratify risk [26]. After analysis of 48,860 patients identified through the American College of Surgeons National Surgical Quality Improvement Project who underwent hepatopancreato-biliary surgery, key risk factors included white race, high body mass index, longer operative time, and transfusion requirement. Although this model can achieve a relatively high negative predictive value, the concordance statistic of 0.63 suggests that further refinement of this model will be necessary to improve its predictive accuracy.

Thromboprophylaxis is generally recommended in the immediate postoperative period after pancreatectomy. Extended prophylaxis with enoxaparin for 4 weeks postoperatively was shown in the ENOXACAN II studies to decrease the rate of VTE by approximately 50% without increasing bleeding rates or other complications [27]. Similar results were seen in the FAME trial with a 4-week course of dalteparin compared with 1 week of thromboprophylaxis [28]. These data have led to consensus guidelines from the American College of Chest Physicians recommending thromboprophylaxis for 4 weeks postoperatively for patients undergoing pancreatectomy (grade 1B evidence) [29].

Thromboprophylaxis in Patients with Metastatic Pancreatic Cancer

Although a consensus has emerged for thromboprophylaxis following definitive pancreatectomy, in the metastatic setting, prophylactic anticoagulation remains controversial. The challenge relates to the difficulty of adequately capturing and measuring risk for an individual patient, making it difficult to know which patients are most likely to benefit from a thromboprophylaxis strategy. Impaired hepatic synthetic function and renal impairment, present in many patients with metastatic disease, can also increase both the risks of thrombosis and bleeding. Some patients with cancer may also require frequent procedures, which can make the use of anticoagulation challenging. Therefore, the choice of which patients should receive prophylactic anticoagulation during treatment for pancreatic cancer remains highly individualized. It is also important to consider that VTE and bleeding risk can fluctuate over a patient's disease course, which can significantly impact assessment of the risks versus benefits of prophylactic anticoagulation. This argues that the risk-benefit equation must be reassessed at intervals in the disease course. In addition, beyond considerations of bleeding versus thrombotic risk, there are other key considerations for patients when deciding on an anticoagulation regimen. For example, when patients with cancer were surveyed regarding the most important factors to them in choosing whether to receive an anticoagulant, interference with cancer treatment ranked first, above concern for risk of recurrent VTE (second), bleeding (third), and preference for oral versus injectable agents (fourth) [30]. Therefore, it is crucial for

Table 3. Key completed clinical trials of thromboprophylaxis in pancreatic cancer

Trial	Patients	Treatment	Enrollment	VTE events (treatment vs. placebo)	Major bleeding events (treatment vs. placebo)	Number needed to treat
Low molecular weight heparin						
Local disease (postoperative)						
Enoxaparin and Cancer II (ENOXACAN II)	Patients with pancreatic cancer undergoing pancreatectomy	Enoxaparin 40 mg subcutaneously for 4 weeks vs. 1 week postoperatively	501	4.8% vs. 12.0%	0.8% vs. 0.4% (N.S.)	14
Fragmin After Major Abdominal Surgery (FAME)	Patients undergoing major abdominal surgery	Dalteparin for 4 weeks vs. 1 week postoperatively	427	7.3% vs. 16.3%	0.5% vs. 1.8% (N.S.)	12
Advanced disease						
FRAGEM	Patients with advanced pancreatic cancer	Gemcitabine plus dalteparin vs. gemcitabine alone for up to 12 weeks	123	12% vs. 28%	3% vs. 3% (N.S)	6
PROSPECT-CONKO 004	Patients with advanced pancreatic cancer receiving chemotherapy	Enoxaparin (1 mg/kg for 1 month, then 40 mg daily) vs. placebo	312	1.3% vs. 10.2%	4.4% vs. 3.3% (N.S.)	11
SAVE-ONCO[a]	Patients with advanced solid tumors receiving chemotherapy	Semuloparin vs. placebo	3,212 (254 with pancreatic cancer)	1.2% vs. 3.4% (2.4% vs. 10.9% for pancreatic cancer)	2.8% vs. 2.0% (N.S.)	12
PROTECHT[a]	Patients with advanced solid tumors receiving chemotherapy	Nadroparin vs. placebo	1,150 (53 with pancreatic cancer)	2.0% vs. 3.9% (5.9% vs. 8.3% for pancreatic cancer)	0.7% vs. 0.0% (N.S.)	42
Direct oral anticoagulants						
AVERT[a]	Patients with advanced solid tumors receiving chemotherapy and Khorana score ≥2	Apixaban vs placebo	563 (77 with pancreatic cancer)	4.2% vs. 10.2%	3.5% vs. 1.8% (p = .046)	17
CASSINI[a]	Patients with advanced solid tumors receiving chemotherapy and Khorana score ≥2	Rivaroxaban vs placebo	841 (274 with pancreatic cancer)	6% vs. 8.8% (N.S.)	2.0% vs. 1.0% (N.S)	35

[a]SAVE-ONCO, PROTECHT, AVERT, and CASSINI studies included patients with advanced solid tumors, including a subset of patients with pancreatic cancer.
Abbreviations: N.S., non-significant; VTE, venous thromboembolism.

providers to consider the potential impact of anticoagulation on the cancer treatment plan when making recommendations to patients weighing risks versus benefits of anticoagulation.

Several important studies have been completed testing the hypothesis that thromboprophylaxis can decrease VTE events in patients with advanced pancreatic cancer (Table 3).

Low-Molecular-Weight Heparin

In the FRAGEM trial, 123 patients in the U.K. with metastatic pancreatic cancer were randomized to gemcitabine plus 12 weeks of dalteparin or gemcitabine alone [31]. Coprimary endpoints were rate of VTE events during the 12-week anticoagulation period and rate of VTE events during the follow-up period. Dalteparin significantly decreased the rate of VTE in both the anticoagulation period (23% vs. 3.4%) and the entire follow-up period (28% vs. 12%). The number needed to treat (NNT) for anticoagulation during the entire follow-up period to prevent one VTE event was six patients. However, the authors included both symptomatic and incidental VTEs in their analysis, potentially limiting the clinical significance of these results. Although the rate of fatal VTE between the two groups was not statistically significant given the small number of events per arm, it is notable that 8.3% of patients in the control arm died of VTE during the study versus 0% in the dalteparin group. Only six patients did not complete the 12 weeks of anticoagulation, with only two patients experiencing severe hemorrhage requiring discontinuation of anticoagulation. The overall bleeding risk in the dalteparin arm was 9% versus 3% in the control arm, with a

number needed to harm of 16. However, serious hemorrhagic complications, defined as overt bleeding requiring transfusion or hemoglobin drop of >2 g/dl, were equivalent in the two groups. There were also no differences in tumor control rates, time to progression, or overall survival between the two groups, although it is worth noting that the study was not powered to detect a significant survival benefit of thromboprophylaxis. Another important consideration when assessing the generalizability of this study is that first-line therapy for pancreatic cancer has changed since completion of this study, with gemcitabine monotherapy infrequently used if a patient can tolerate the combination chemotherapy regimens shown to improve overall survival [32–34].

The second pivotal trial that investigated concurrent thromboprophylaxis in patients with pancreatic cancer receiving chemotherapy was the CONKO-004 trial [34]. In this prospective, open-label, multicenter trial, patients were randomized to either chemotherapy alone or chemotherapy plus enoxaparin daily. It is important to consider that patients in the enoxaparin arm of this study received a dose of 1 mg/kg of enoxaparin daily for the first 3 months, followed by 40 mg daily thereafter. Given that standard prophylactic dosing of enoxaparin in the U.S. is 40 mg daily, it may be challenging to extrapolate findings from CONKO-004 to this enoxaparin dose. The primary outcome was rate of symptomatic VTE within 3 months, and secondary outcomes included progression-free survival (PFS), overall survival (OS), overall symptomatic VTEs within 3 months, and bleeding rate. CONKO-004 showed that there was a reduction in symptomatic VTE at 3 months from 10.2% in the control arm to 1.3% in the enoxaparin arm, with an NNT of approximately 11. There was no difference in rates of major bleeding between the two groups. There were three fatal bleeding events, but two were in the observation arm. The one patient with a fatal bleed in the treatment arm occurred in the setting of esophageal varices. However, despite the decrease in symptomatic VTE rate, there was no difference in PFS or OS between the two groups.

Other low-molecular-weight heparins, including semuloparin (SAVE-ONCO Trial) and nadroparin (PROTECHT Trial) [35–37], have been investigated as thromboprophylaxis in advanced solid tumors. In the SAVE-ONCO Trial, 3,212 patients with metastatic or locally advanced cancer being treated with chemotherapy were randomized to semuloparin or placebo with a primary endpoint of rate of symptomatic VTE and a secondary endpoint of overall survival. Although there was a statistically significant difference in symptomatic VTE between treated and untreated patients, semuloparin was rejected by the U.S. Food and Drug Administration given the very low absolute risk reduction (2.2%), high rate of early censoring, and lack of difference in overall survival. However, in the subgroup of 254 patients with pancreatic cancer, there appeared to be much higher absolute risk reduction (8.5%), from 10.9% VTE incidence in the placebo control to 2.4% in the treated arm, which is likely reflective of the particularly high baseline thrombotic risk seen in patients with pancreatic cancer. Similarly, in the PROTECHT Trial, 1,150 patients with cancer were randomized to nadroparin or placebo, with a primary outcome of symptomatic VTE. Nadoparin also showed a low but statistically significant absolute risk reduction of 1.9% (3.9% with placebo vs. 2.0% with nadroparin) in patients with solid tumor malignancies. However, there was no benefit for the subgroup of 53 patients with pancreatic cancer. Several meta-analyses have similarly shown decreased VTE risk but without a survival benefit [38, 39]. Based on the results of these studies, the National Comprehensive Cancer Network assigned a category 2A (a uniform consensus despite lower-level evidence) recommendation for prophylactic low-molecular-weight heparin for patients with locally advanced or metastatic pancreatic cancer who are receiving chemotherapy [40].

Direct Oral Anticoagulants

The efficacy of several direct oral anticoagulants (DOACs) to treat acute VTE is now well established. For example, edoxaban was shown to be noninferior to dalteparin in terms of composite recurrent VTE and major bleeding risk in the Hokusai VTE Cancer Trial. There were also slight differences in recurrent VTE and bleeding risk between edoxaban and dalteparin, with less recurrent VTE overall in the edoxaban group but increased bleeding risk [41]. Preliminary data from the ADAM VTE Trial and SELECT-D Trial similarly show decreased risk of recurrent VTE without increased major bleeding risk when using apixaban or rivaroxaban, respectively, compared with dalteparin [42, 43]. However, there did appear to be increased risk of clinically relevant nonmajor bleeding with DOAC use compared with dalteparin, an important consideration when assessing bleeding risk for patients.

However, until recently, few studies evaluated the role of DOACs as thromboprophylaxis in patients with cancer. A significant advantage of DOACs is that they can be administered orally, potentially improving patient adherence, convenience, and quality of life. The phase III AVERT Trial was designed to determine whether apixaban has efficacy as thromboprophylaxis for patients with cancer with intermediate-to-high Khorana scores (≥2) [44]. A total of 563 patients were randomized to either apixaban 2.5 mg twice per day or placebo. The primary outcome of the study was VTE within the first 180 days of follow-up. During the follow-up period, there was a statistically significant decrease in VTE events in the apixaban (4.2% vs. 10.2%), with NNT of 17. There was an increase in major bleeding risk with apixaban compared with placebo (3.5% vs. 1.8%), with 3 of 15 major bleeding episodes considered to be a clinical emergency. However, there were no deaths attributed to bleeding. Although the authors do not report subgroup analysis by cancer type, the AVERT study included a significant proportion of patients with pancreatic cancer (77 of 563), suggesting that the findings are generalizable to this patient population. In a similarly designed study (CASSINI Trial), 841 patients, 274 with pancreatic cancer, with Khorana scores ≥2 were randomized to either rivaroxaban 10 mg daily or placebo for up to 180 days [45]. The composite primary endpoint of this study included both symptomatic and asymptomatic VTE at 180 days following randomization. There was a trend toward a decrease in VTE events with rivaroxaban compared with placebo (6% vs. 8.7%), with NNT of 35, although this was not statistically significant. These results were likely due in part to the fact that a significant proportion of patients in the trial did not complete 180 days of rivaroxaban. In a prespecified secondary analysis, rivaroxaban reduced VTE risk during the time patients were taking the drug. Major bleeding events occurred in 2.7%

of patients treated with rivaroxaban versus 1% in the placebo group. In this study, pancreatic cancer was the most common tumor type (32.6% of patients). Specifically, in the pancreatic cancer population, there was a statistically significant reduction in risk of VTE during the intervention period (10.1% vs. 3.7%). However, similar to the results of the overall study population, there was no significant difference in VTE events during the 180 day follow-up period (the prespecified primary endpoint) in the pancreatic cancer patient subgroup [46]. Therefore, these results should be interpreted with caution. A significant limitation of this study is that the primary endpoint included both symptomatic and asymptomatic VTE events. The study was designed to capture more asymptomatic events through screening lower extremity ultrasounds every 8 weeks. Because incidentally found VTE is not necessarily clinically significant, it is unclear whether changes in the rate of asymptomatic VTE actually benefit patients.

Another unique factor to consider when deciding whether to start DOACs in patients with gastrointestinal (GI) malignancies is the observed increased risk of GI bleeds in patients on DOACs compared with other anticoagulants. This is due in part to uptake of DOACs in the GI tract and possibly excessive local effect [47]. In the recently published pivotal trials of edoxaban and rivaroxaban for the treatment of cancer-associated VTE, there was increased bleeding risk associated with these agents compared with low-molecular-weight heparin [41, 43]. However, this increased bleeding risk was primarily driven by upper GI bleeds occurring in patients with GI malignancies. Whether this risk can be extrapolated to prophylactic dosing or to pancreatic cancer in particular remains unclear but highlights the importance of individualizing the treatment approach to thromboprophylaxis in patients with cancer and being particularly cautious in patients with structural problems, esophageal varices, altered upper GI motility, tumor invasion, or obstruction who may be at elevated risk of GI bleeding.

Further complicating the appropriate selection of an agent in patients with pancreatic cancer, DOACs have variable metabolism and elimination, requiring significant caution when used in patients with renal and hepatic impairment. In addition, there are significant risks of drug-drug interactions with these agents. For example, apixaban is a substrate for P-glycoprotein (P-gp) and a CYP3A4 inducer should be avoided. Therefore, in patients with cancer who are frequently on complex medication regimens including novel agents that may involve the P-gp and CYP3A4 pathways, it is essential for physicians to carefully assess potential drug-drug interactions before initiation of DOACs.

A significant limitation of all of these studies is that they did not show a survival benefit with thromboprophylaxis. For low-molecular-weight heparin, given that daily injections with either dalteparin or enoxaparin are associated with significant patient discomfort and cost, clinicians have to consider what level of evidence is necessary to implement thromboprophylaxis in their patients with pancreatic cancer. DOACs offer less burden on patients with similar benefit, which could change patient and physician decision making when considering risks versus benefits. Another important factor when assessing potential benefits of thromboprophylaxis is whether patients can be successfully treated with therapeutic anticoagulation once VTEs occur without significant impact on morbidity or mortality. If there is no difference in outcome between using anticoagulation preventatively versus therapeutically, waiting until a VTE occurs may be preferable because it would decrease the number of patients treated unnecessarily. However, it is likely that thrombosis and bleeding events are not equivalent outcomes, with fatal thrombotic events more likely to be associated with increased morbidity compared with bleeding events. It is important to note that none of the discussed studies were powered to detect a difference in overall survival. Another caveat when assessing the generalizability of these studies is the exclusion of patients with brain metastases. Dedicated studies assessing the risks versus benefits of anticoagulation in such patients remain a critical area of unmet need. Last, it is important to assess competing risk when evaluating the clinical relevance of these studies. Given that pancreatic cancer continues to be associated with an extremely poor prognosis, death from pancreatic cancer may outweigh the risk of death from VTE. However, as outcomes improve for pancreatic cancer patients in the future, it will be important to consider the effect of this competing risk. As cancer survival improves, the benefits of anticoagulation may become more apparent [48].

Changing Risk Versus Benefit Equation in Patients with Pancreatic Cancer

Finally, as newer agents enter the armamentarium for the treatment of pancreatic cancer, clinicians and researchers will need to reassess the risk versus benefit of thromboprophylaxis for these patients. For example, recently published data using the pegylated recombinant human hyaluronidase, pegvorhyaluronidase alfa (PEGPH20), demonstrated promising efficacy when combined with gemcitabine plus nab-paclitaxel [49]. Because of an increased rate of thromboembolic events during stage 1 of the study in patients treated with PEGPH20 compared with controls (43% vs. 25%), enoxaparin at a dose of 1 mg/kg per day was added to both arms of the study. Not surprisingly, the addition of enoxaparin to the control gemcitabine/nab-paclitaxel arm also led to a significant reduction in thromboembolic events (25% vs. 6% after the study was amended to include enoxaparin), lending further support that the benefits of thromboprophylaxis may extend to current standard-of-care chemotherapy regimens [49]. Another ongoing pilot study is specifically assessing the thrombosis rate of gemcitabine plus nab-paclitaxel plus PEGPH20 plus prophylactic dose rivaroxaban with a primary endpoint of symptomatic thromboembolic events at 1 year of follow-up (NCT02921022).

Conclusion

So where does this all leave the clinician, faced with the daunting task of considering the risks and benefits of thromboprophylaxis for a patient with pancreatic cancer? First, although it is well established that pancreatic cancer is associated with a significant risk of VTE, identification of additional features that define this risk within the population of patients with pancreatic cancer remains challenging and

needs further investigation. In the postoperative period, extended thromboprophylaxis for at least 4 weeks is now well established. It should be considered in the neoadjuvant setting as well, to increase opportunity for surgical resection. However, the role of prophylactic anticoagulation in the metastatic setting is less well defined. Although several important scoring systems, including the Khorana score and PROTECHT score, assess VTE risk for patients with cancer, the positive predictive value of these scoring systems is limited. Also, these scoring systems were not specifically designed to assess risk in patients with pancreatic cancer, who represent a very different population than the majority of patients with cancer. Additional key considerations crucial for clinicians to take into account include thrombotic risk factors other than malignancy (e.g., history of VTE and other hypercoagulable states) and bleeding risk factors (e.g., history of variceal or diverticular bleeding), as well as the potential impact of anticoagulation on the patient's cancer therapy regimen. A definitive pancreatic cancer-specific scoring system, potentially integrating CA 19-9 or circulating microparticles, remains an unmet need. Although several large trials have been completed that show that anticoagulation reduces the incidence of symptomatic VTE in patients with pancreatic cancer without significantly increasing bleeding risk, whether this leads to any improvement in morbidity or mortality is unknown. Incorporating the risk of VTE associated with novel therapeutic agents for pancreatic cancer and carefully accounting for individual patient perspectives on bleeding versus thrombosis risk are other important considerations when deciding whether to start thromboprophylaxis. Last, cost and insurance coverage frequently dictate choice between anticoagulants in clinical practice and must be considered when patients and physicians select an appropriate anticoagulation regimen.

It is not possible to make uniform recommendations about the role of thromboprophylaxis in pancreatic cancer, particularly in the metastatic settings. However, it is likely that a subset of patients would benefit from thromboprophylaxis, and the treating physician at this time must intuit those who are at highest risk of VTE and low risk of bleeding. As patients with pancreatic cancer live longer, and we learn more from well-designed clinical trials, physicians will need to reassess whether the benefits outweigh the risks of long-term prophylactic anticoagulation and discuss these issues with their patients to make informed decisions.

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